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Targeting class I histone deacetylase in renal tubular epithelial cells inhibits priming inflammatory responses

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Objectives: Renal tubular epithelial cells (RTECs) contribute to immunopathology during kidney inflammation. However, new way for the regulation of their function remains inadequate. Here, we investigated the role of histone deacetylases (HDACs) in RTECs in response to inflammatory stimuli and their blockade effect.

Methods: Human renal proximal tubular epithelial cell line HK-2 was cultured in the presence or absence of recombinant interferon gamma (IFN-g) 200 U/ml plus tumor necrosis factor alpha(TNF-a) 5 ng/ml. The HDAC activity was determined on the expression levels of acetylated H3 and a-tubulin by immune blot assay. To determine the functional activity of HDAC inhibitor SB939, we analyzed the immune stimulatory phenotype of HK-2 cells such as class II MHC molecule, CD80, CD86, and CD40 by flow cytometry. In addition, the culture supernatants were used for measuring cytokines and chemokines by ELISA assay.

Results: We found that class I HDACs were constitutively activated in HK-2 cells. Whereas, HDAC6 activity was induced by treatment of IFN-g/TNF-a within 12 h. Treatment of pan-inhibitor SB939 in HK-2 cells completely prevented HDAC activity which was induced by IFN-g/TNF-a treatment. Noticeably, SB939 significantly inhibited up-regulation of CD40 and CD80 expression induced by IFN-g/TNF-a treatment. Moreover, MCP-1 production was also significantly suppressed. Class I inhibitor MS275 selectively inhibited class I HDAC activity without impairment of HDAC 6 activity and effectively suppressed the inflammatory capacity of the cells stimulated with IFN-g/TNF-a. However, HDAC6 specific inhibitor tubastatin A did not show the inhibitory effects.

Conclusions: Our results demonstrate that class I HDAC activity is involved in RTECs in response to IFN-g/TNF-a, which facilitates T cell-mediated inflammatory responses and suggest that pan/class I HDAC inhibitor has a therapeutic potential for the inhibition of T cell-mediated inflammation in kidney such as renal transplantation.